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(64) Rapidly releasable microcapsules and method for the preparation thereof.

(57) Novel rapidly releasable microcapsules containing a core material, the coating walls of which consist essentially of ethylcellulose and a water-soluble material which can be dissolved in water and an acidic aqueous solution, and a method for the preparation thereof. The microcapsules can rapidly release the active ingredient contained therein as a core material in gastric and intestinal tracts.

EP 0 076 515 A1

RAPIDLY RELEASABLE MICROCAPSULES AND
METHOD FOR THE PREPARATION THEREOF

The present invention relates to novel rapidly
releasable microcapsules and a method for the preparation
5 thereof, more particularly to an ethylcellulose micro-
capsules containing a core material, the coating walls
of which consist essentially of ethylcellulose and a
water-soluble material, which can rapidly release the
active compound (the core material) in gastric and
10 intestinal tracts.

It is known to control the release of a core
material in microcapsules by thickening the coating
walls of microcapsules or by forming compact coating
walls and thereby decreasing the permeability thereof
15 (cf. Tamotsu Kondo and Masumi Koishi; "Microcapsules,
Process for the Preparation thereof, Their Properties
and Applications", issued by Sankyo Shuppan, 1977).
According to these known methods, however, while the
release of core material is well controlled, the release
20 of core material is also inhibited even when the core
material should be released and hence the desired activities
of the main active compounds are occasionally not obtained.
Particularly, in case of pharmaceutical compounds, they
are usually microencapsulated with ethylcellulose in order
25 to mask unpleasant odor or taste thereof, but in most

cases, such microcapsules show retarded release of the active ingredient in stomach.

From this viewpoint, the present inventors have extensively studied on improvement of microcapsules, and as a result, it has been found that the desired rapidly releasable microcapsules having excellent effect of protecting the core material and being capable of releasing easily the core material in gastric and intestinal tracts can be obtained by incorporating a water-soluble material into the ethylcellulose coating walls of microcapsules containing core material.

An object of the present invention is to provide rapidly releasable microcapsules being capable of releasing rapidly the active component (core material) in gastric and intestinal tracts when administered. Another object of the invention is to provide a process for the preparation of the rapidly releasable microcapsules. These and other objects and advantages of the present invention will be apparent to persons skilled in the art from the following description.

The novel rapidly releasable microcapsules of the present invention can be prepared by dispersing a core material in a solution containing ethylcellulose as a coating wall-forming material, and then forming ethylcellulose coating walls on and around the particles of the core material by phase-separation of ethylcellulose.

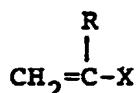
The core material used in the present invention includes pharmaceutical compounds and foodstuffs which may be in the form of a solid, gel or semi-solid. The particle size of the core material is not critical but is usually in the range of about 30 to 1,000 μ , preferably about 50 to 500 μ .

Ethylcellulose used for forming microcapsule coating walls on and around the particles of the core material has preferably an ethoxy content of about 46.5 to 55 W/W % and a viscosity of about 3 to 500 cP (the viscosity of ethylcellulose is measured in a 5 W/W % solution in toluene-ethanol (4 : 1) at 25°C). The ethylcellulose is usually used in an amount of about 0.01 to 10 grams per gram of the core material.

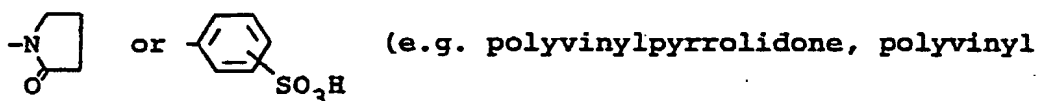
The water-soluble material to be incorporated into the ethylcellulose coating walls includes all substances which can be dissolved in water and an acidic aqueous solution, preferably be dissolved in a concentration of at least about one W/V % in water at about 20 to 40°C and an acidic aqueous solution having a pH about 1.2.

Examples of the water-soluble material are disaccharides (e.g. lactose, sucrose); sugar alcohols (e.g. mannitol); polysaccharides containing 10 W/W % or more of sulfonic group in the molecule (e.g. carrageenan); hydroxyalkylcelluloses (e.g. hydroxypropylcellulose); hydroxyalkyl alkylcelluloses (e.g. hydroxypropyl methylcellulose); organic dibasic or tribasic acids or their

salts (e.g. tartaric acid, sodium fumarate, citric acid);
inorganic acid salts (e.g. potassium sulfate, potassium
dihydrogen phosphate, ammonium phosphate, potassium
metaphosphate); amino acids or their salts (e.g. sodium
5 glutamate, alanine, lysine hydrochloride); nucleotides
or their salts (e.g. 5'-inosinic acid, sodium 5'-uridyate);
polymers composed of a monomer of the formula:



10 wherein R is hydrogen atom or methyl group, and X is
carboxy group, hydroxy group, or a group of the formula:



15 alcohol, sodium polyacrylate, polymethacrylic acid,
polystyrenesulfonic acid); gum arabic; methylcellulose;
polyethylene oxide; gelatin; sodium chloride; and coffee
powder.

These water-soluble materials are preferably
20 in the form of a finely-divided particle, particularly
having a particle size of about 300 μ or less. The
water-soluble materials are preferably used in an
amount of at least about 0.01 gram, more preferably
about 0.05 to 20 grams per gram of the coating wall-
25 forming material (ethylcellulose).

In the preparation of the microcapsules
of the present invention, an ethylcellulose dispersion

containing a core material is firstly prepared by dispersing a core material into a solution containing ethylcellulose as the wall-forming material.

5 The solvent for dissolving ethylcellulose is a substance which can dissolve ethylcellulose with heating (i.e. at a temperature of 70 to 80°C) but does not dissolve under cooling and further does not dissolve both of the core material and the water-soluble material. Suitable examples of the solvent
10 are cyclohexane, a mixture of cyclohexane and n-hexane, or the like, among which cyclohexane is particularly suitable. Ethylcellulose is dissolved in such a solvent at a temperature of 75 to 80°C. The ethylcellulose solution thus obtained has preferably a concentration
15 of ethylcellulose of about 0.1 to 10 W/W %, more preferably about 1 to 5 W/W %. The dispersion of a core material into an ethylcellulose solution is preferably carried out with stirring at a temperature of about 75 to 80°C.

20 The phase-separation of ethylcellulose from the dispersion containing a core material is carried out in the presence or absence of a phase-separation-inducing agent, i.e. by either coacervation or flocculation, and optionally in the presence of a wall-forming
25 auxiliary and/or a surfactant.

 The phase-separation-inducing agent includes

polyethylene, butyl rubber, polyisobutylene, and polybutadiene. The wall-forming auxiliary includes dimethyl polysiloxane, methylphenyl polysiloxane, diphenyl polysiloxane and polystyrene-polydimethyl polysiloxane block copolymer. The surfactant includes an ester of C₁₂₋₁₈ fatty acid with sorbitan (e.g. sorbitan monolaurate, sorbitan sesquilaurate, sorbitan trilaurate, sorbitan monooleate), an ester of C₈₋₁₈ fatty acid with glycerin (e.g. glycerin monocaprylate, glycerin monolaurate, glycerin monooleate), a phospholipid (e.g. soybean phospholipid, egg-yolk phospholipid), calcium stearyl lactate, an ester of C₈₋₁₈ fatty acid with propylene glycol (e.g. propylene glycol monocaprylate, propylene glycol distearate), and an ester of C₁₂₋₁₈ fatty acid with sucrose (e.g. sucrose monostearate, sucrose distearate, sucrose tristearate). These additives may be added to the ethylcellulose solution when ethylcellulose is dissolved. The additives are used in a concentration of about 0.01 to 10 W/V % (phase-separation-inducing agent), about 0.01 to 10 W/V % (wall-forming auxiliary), and about 0.001 to 10 W/V % (surfactant), respectively.

The phase-separation of ethylcellulose is preferably carried out by cooling the dispersion at a rate of about 0.05 to 4°C/minute, especially 0.1 to 2°C/minute. When a water-soluble material is incorporated into the ethylcellulose coating walls, it is added with stirring to the dispersion before cooling or during the cooling step, particularly at the stage where coating

walls of ethylcellulose in the form of "gel" is formed on and around the particles of the core material and the thus-formed coating walls have still fluidity in some extent (i.e. have a viscosity of 0.1 to 50 P, especially 1 to 10 P). More especially, since the coating walls having a fluidity is formed on an around the core material by cooling the dispersion to about 55 to 75°C, especially about 65°C (while it may somewhat vary depending on the scale of method and cooling rate, etc.), it is preferable to add the water-soluble material to the dispersion when cooled to said temperature. The water-soluble material thus added is appropriately penetrated and dispersed into the coating walls. After adding the water-soluble material, the dispersion is further cooled to a temperature not higher than 40°C (e.g. 30 to 20°C), and thereby, the formed embryonic microcapsules are shrunk and become solid by solvent loss from the coating walls, thus giving stable ethylcellulose microcapsules.

The microcapsules thus obtained may be recovered in conventional manner, such as decantation, centrifugation, filtration and so forth, wherein the microcapsules do not adhere or coagulate each other. The microcapsules thus recovered may, if required, be washed with a solvent such as cyclohexane, petroleum ether, n-hexane, etc. and then dried in conventional manner (e.g. by a hot-air drying method or heat transfer drying method).

The microcapsules of the present invention can be applied to not only pharmaceutical medicaments but also other various substances such as veterinary drugs, foodstuffs, or the like. The pharmaceutical medicaments, to which the microcapsules of the present invention and the process for the preparation thereof can be applied, are, for example, vitamins (e.g. ascorbic acid), amino acids (e.g. potassium aspartate, magnesium aspartate), peptides (e.g. insulin), chemotherapeutics (e.g. sulfamethizole), antibiotics (e.g. benzylpenicillin potassium salt), respiratory stimulants (e.g. dimeflin hydrochloride), antitussives and expectorants (e.g. tipecidine dibenzoate, bromhexine hydrochloride, trimetoprim hydrochloride), anti-tumor agents (e.g. 5-fluorouracil, bleomycin hydrochloride), autonomic agents (e.g. N-butylscopolaminium bromide), neuro-psychotropic agents (e.g. calcium N-(γ,γ -dihydroxy- β,β -dimethylbutyryl)- γ -aminobutyrate), local anesthetics (e.g. oxethazone), muscle relaxants (e.g. phenprocoumon), agents affecting digestive organs (e.g. methylmethionine sulfonium chloride, 1,1-dimethyl-5-methoxy-3-(dithien-2-ylmethylene)piperidinium bromide, precipitated calcium carbonate, trimethoprim maleate), anti-histaminics (e.g. diphenhydramine hydrochloride), antidotes (e.g. D-penicillamine, difenoxamine mesylate), hypnotics and sedatives (e.g. flurazepam hydrochloride), antiepileptics (e.g. sodium valproate), antipyretics, analgesics and

anti-inflammatory agents (e.g. acetylsalicylic acid,
indometacin, naproxen), cardiotonics (e.g. digoxin,
proscillaridin), antiarrhythmic agents (e.g. oxprenolol
hydrochloride), diuretics (e.g. penfluzide), vasodi-
5 lators (e.g. diltiazem hydrochloride), antilipaemics
(e.g. sodium dextran sulfate), nutrients, tonics and
alteratives (e.g. calcium L-aspartate), anticoagulants
(e.g. heparin calcium), agents for liver disease (e.g.
phosphorylcholine chloride calcium salt), antidiabetic
10 agents (e.g. carbutamide), antihypertensives (e.g.
clonidine hydrochloride), or the like.

When the microcapsules of the present invention
are administered, the water-soluble material incorporated
into the ethylcellulose coating walls is rapidly dissolved
15 in water and thereby the microcapsules become porous and
then water or other liquid easily penetrates inside the
microcapsules, by which the active compound contained
therein is rapidly released. Accordingly, in the micro-
capsules of the present invention, the releasing rate of
20 the active compound can be controlled by controlling the
addition amount of the water-soluble material. Besides,
although the conventional microcapsules consisting of
only ethylcellulose requires a fixed period of time
until gastric juice penetrates into the coating walls
25 in stomach, the microcapsules of the present invention
can rapidly release the core material within a short
period of time after administration, because the coating

walls of the microcapsules become porous by contact with gastric juice in stomach. In addition to the above advantages, the microcapsules of the present invention have an appropriately improved ethylcellulose coating walls by incorporating a water-soluble material into the coating walls, by which the microcapsules show excellent compatibility with various carrier and also excellent fluidity and further the microcapsules can easily be tabletted without undesirable sticking or capping. The microcapsules of the present invention show also less unpleasant feeling when administered.

The present invention is illustrated by the following Experiments and Examples, wherein "part" means "part by weight" unless specified otherwise. Throughout the specification and claims, the terms "alkyl" should be interpreted as referring to alkyl having one to 4 carbon atoms.

Experiment I

Microcapsules containing trimebutine maleate (chemical name: 2-dimethylamino-2-phenylbutyl-3,4,5-trimethoxybenzoate hydrogen maleate) (a water-soluble material being incorporated into the coating walls as a release-controlling material) were prepared according to the following methods. Then, the yield of microcapsules thus obtained, the amount of the trimebutine maleate contained in the microcapsules, and the 50 % release time (T_{50}) (i.e. a period of time which was

necessary to release 50 % of the active ingredient from the microcapsules) in water were examined, respectively.

Method

(i) Core material:

5 To a powdery mixture of trimebutine maleate (23.3 parts) and lactose (73.7 parts) was added a solution of methylcellulose (3 parts) in water (15 parts), and the mixture was kneaded in a usual manner to form granules. The granules were dried and regulated
10 to a particle size of 105 to 350 μ .

(ii) Preparation of microcapsules:

Soybean phospholipid (0.8 g) and a silicone resin (conformable to the requirements of 4th Official Compendium of Food Additives in Japan, i.e. a mixture
15 of dimethyl polysiloxane (viscosity: 100 to 1,100 cSt at 25°C) and 3 to 15 % by weight of silicon dioxide) (24 g) were dissolved in cyclohexane (800 ml) and thereto was added ethylcellulose (ethoxy content: 48 %, viscosity: 100 cP) (20 g) and the mixture was dissolved
20 by heating at 80°C. After dispersing a core material (100 g) to the solution, the dispersion was cooled with stirring at 400 r.p.m. When the temperature became to about 65°C, finely divided particles of a water-soluble material (100 g) as shown in the following Table 1 were
25 added in order to incorporate them into the coating walls and then the mixture was cooled to room temperature. The microcapsules thus formed were separate, washed with n-hexane and dried. Said microcapsules were passed

through JIS (Japanese Industrial Standard) standard
sieves (500 μ and 105 μ aperture) to give trimebutine
maleate-containing microcapsules which met the re-
quirements of "fine granules" specified in the Pharma-
5 copoeia of Japan 10th-Edition.

As a reference, microcapsules were prepared
in the same manner as described above except that no
water-soluble material was added.

(iii) Results:

10 The results are shown in Table 1. As is clear
from the results, when the water-soluble material was
incorporated into the coating walls, the release of
the active ingredient was promoted.

Table 1

Water-soluble material	Microcapsules		
	Yield (g)	Content of active ingredient (%)	T ₅₀ (minute)
Lactose	212	11.2	14
Sucrose	205	10.6	20
Mannitol	211	11.3	13
Sodium glutamate	203	10.8	17
Citric acid	198	10.7	15
Polyvinyl-pyrrolidone	200	10.7	11
Polyvinyl alcohol	203	10.6	17
Methylcellulose	199	10.9	14
Hydroxypropyl-cellulose	197	10.6	16
Hydroxypropyl methylcellulose	199	11.1	14
Polyethylene oxide	204	10.8	15
Sodium polyacrylate	203	11.2	13
Gum arabic	201	11.0	19
Gelatine	199	10.8	19
- (reference)	101	19.9	78

Experiment II

Microcapsules containing 1-methyl-5-methoxy-3-(dithien-2-ylmethylene)piperidium hydrobromide (I) (a water-soluble material being incorporated into the coating walls as a release-controlling material) were prepared, and the yield of microcapsules, the amount of the active ingredient contained in the microcapsules, and T_{50} in water were examined, likewise.

Method

10 (i) Preparation of microcapsules:

To cyclohexane (1600 ml) were added the same silicone resin as used in Experiment I (48 g) and the same ethylcellulose as used in Experiment I (40 g), and the mixture was dissolved by heating at 80°C. After dispersing the above active compound (I) (particle size: 105 - 210 μ) (120 g) to the solution, the dispersion was cooled with stirring at 300 r.p.m. When the temperature became to about 65°C, finely divided particles (240 g) of a water-soluble material as shown in Table 2 in order to incorporate it into the coating walls and then the mixture was cooled to room temperature. The microcapsules thus formed were passed through JIS standard sieves (350 μ and 105 μ aperture) to give the active compound (I)-containing microcapsules which met the requirements of powders.

As a reference, microcapsules were prepared in the same manner as described above except that no water-soluble material was added.

(ii) Results:

5 The results are shown in Table 2. As is clear from the results, when a water-soluble material was incorporated into the coating walls, the release of the active ingredient was promoted.

Table 2

Water-soluble material	Microcapsules		
	Yield (g)	Content of active ingredient (%)	T ₅₀ (minute)
Tartaric acid	392	30.2	14
Sodium fumarate	389	30.4	31
Sodium chloride	378	30.8	21
Potassium sulfate	381	30.1	37
Potassium dihydrogen phosphate	387	30.5	23
Ammonium phosphate	391	30.1	28
Alanine	386	30.5	7
Lysine hydrochloride	384	30.9	8
5'-Inosinic acid	383	30.5	13
Sodium 5'-uridyate	373	30.5	9
Potassium metaphosphate	393	30.1	25
Coffee powder	377	30.7	14
(reference)	154	75.1	62

Example 1

Ethylcellulose (ethoxy content: 48 %, viscosity: 100 cP) (16 g) and polyisobutylene (molecular weight: about 800,000) (24 g) were dissolved in cyclohexane (800 ml) with heating. After dispersing trimebutine

maleate-containing core material [prepared in the same manner as described in Experiment I-(i)] (80 g) into the solution, the dispersion was cooled with stirring at 300 r.p.m. When the temperature became to about 65°C, sucrose (80 g) was added in order to incorporate it into the coating walls and then the mixture was cooled to room temperature. The microcapsules thus formed were separated, washed with n-hexane and dried. Said microcapsules were passed through JIS standard sieves (500 μ and 105 μ aperture) to give trimebutine maleate-containing microcapsules (150 g) which met the requirements of "fine granules".

This product had a trimebutine maleate content of 12.3 % and T_{50} in water of 17 minutes.

Example 2

In the same manner as described in Example 1 except that polyethylene (molecular weight: 7,000) (24 g) was used instead of polyisobutylene, there were obtained trimebutine maleate-containing microcapsules (153 g) which met the requirements of "fine granules".

This product had a trimebutine maleate content of 11.9 % and T_{50} in water of 13 minutes.

Example 3

In the same manner as described in Example 1 except that butyl rubber [Mooney viscosity: 67 (ML-8/100°)] (24 g) was used instead of polyisobutylene, there were obtained trimebutine maleate-containing microcapsules

(149 g) which met the requirements of "fine granules".

This product had a trimebutine maleate-content of 12.1 % and T_{50} in water of 8 minutes.

Example 4

5 In the same manner as described in Example 1 except that gelatine (80 g) was used instead of sucrose, there were obtained trimebutine maleate-containing microcapsules (153 g).

Example 5

10 In the same manner as described in Example 1 except that carrageenan (80 g) was used instead of sucrose, there were obtained trimebutine maleate-containing microcapsules (162 g).

Example 6

15 In the same manner as described in Example 1 except taht polymethacrylic acid (80 g) was used instead of sucrose, there were obtained trimebutine maleate-containing microcapsules (154 g).

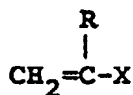
Example 7

20 In the same manner as described in Example 1 except that polystyrenesulfonic acid (80 g) was used instead of sucrose, there were obtained trimebutine maleate-containing microcapsules (163 g).

CLAIMS

1. In ethylcellulose microcapsules comprising (i) particles of a core material and (ii) ethylcellulose coating walls deposited on and around said particles of the core material, the improvement wherein a water-soluble material is incorporated into the ethylcellulose coating walls of the microcapsules.

2. The microcapsules according to claim 1, wherein the water-soluble material is a member selected from the group consisting of a disaccharide; a sugar alcohol; a polysaccharide containing 10 W/W % or more of sulfonic group in the molecule; a hydroxyalkylcellulose; a hydroxyalkyl alkylcellulose; an organic dibasic acid or its salt; an organic tribasic acid or its salt; an inorganic acid salt; an amino acid or its salt; a purine nucleotide or its salt; a polymer composed of a monomer of the formula:



wherein R is hydrogen atom or methyl group, and X is carboxy group, hydroxy group, or a group of the formula:



ethylene oxide; gelatine; sodium chloride; and coffee powder.

3. The microcapsules according to claim 1, wherein the water-soluble material is a member selected

from the group consisting of lactose, sucrose, mannitol, carrageenan, hydroxypropylcellulose, hydroxypropyl methylcellulose, tartaric acid, sodium fumarate, citric acid, potassium sulfate, potassium dihydrogen phosphate, ammonium phosphate, potassium metaphosphate, sodium glutamate, alanine, lysine hydrochloride, 5'-inosinic acid, sodium 5'-uridylate, polyvinylpyrrolidone, polyvinyl alcohol, poly(sodium acrylate), polymethacrylic acid, polystyrenesulfonic acid, gum arabic, methylcellulose, polyethylene oxide, gelatine, sodium chloride, and coffee powder.

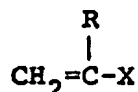
4. A method for the preparation of microcapsules, which comprises

- (i) dissolving ethylcellulose in a solvent,
- (ii) dispersing particles of a core material in the solution,
- (iii) forming the ethylcellulose coating walls on and around the particles of the core material by phase-separation of ethylcellulose in the presence of a water-soluble material, and
- (iv) recovering the thus-formed microcapsules therefrom.

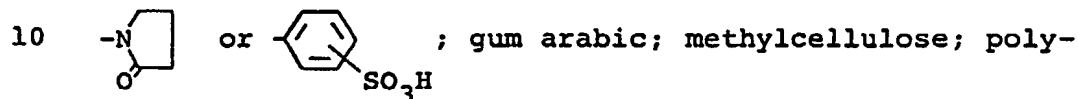
5. The method according to claim 4, wherein the water-soluble material is a member selected from the group consisting of a disaccharide; a sugar alcohol; a polysaccharide containing 10 W/W % or more of sulfonic group in the molecule; a hydroxyalkylcellulose; a hydroxy-

alkyl alkylcellulose; an organic dibasic acid or its salt; an organic tribasic acid or its salt; an inorganic acid salt; an amino acid or its salt; a purine nucleotide or its salt; a polymer composed of a monomer of the

5 formula:



wherein R is hydrogen atom or methyl group, and X is carboxy group, hydroxy group, or a group of the formula:



ethylene oxide; gelatine; sodium chloride; and coffee powder.

6. The method according to claim 4, wherein
15 the water-soluble material is a member selected from the group consisting of lactose, sucrose, mannitol, carrageenan, hydroxypropylcellulose, hydroxypropyl methylcellulose, tartaric acid, sodium fumarate, citric acid, potassium sulfate, potassium dihydrogen
20 phosphate, ammonium phosphate, potassium metaphosphate, sodium glutamate, alanine, lysine hydrochloride, 5'-inosinic acid, sodium 5'-uridylate, polyvinylpyrrolidone, polyvinyl alcohol, sodium polyacrylate, polymethacrylic acid, polystyrenesulfonic acid, gum arabic, methyl-
25 cellulose, polyethylene oxide, gelatine, sodium chloride, and coffee powder.

7. The method according to claim 4, 5 or 6, wherein the solvent is cyclohexane.



European Patent
Office

EUROPEAN SEARCH REPORT

0076515

Application number

EP 82 10 9196

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 7)
X	--- CHEMICAL ABSTRACTS, vol. 94, no. 8, February 1981, page 362, no. 52812b, Columbus Ohio (USA); C.B.LIPPOLD et al.: "Control of drug liberation from microcapsules. Part 1. Legal modification for drug transport through additive-containing lipophilic membranes". & PHARM. IND. 1980, 42(7), 745-52. *Abstract*	1,2,3	B 01 J 13/02 A 61 K 9/52
X	--- US-A-3 960 757 (MASATAKA MORISHITA) *Column 3, lines 57-68; column 4, lines 1-31; column 5, lines 47-55*	1,2,3, 4,5,6	
A	--- US-A-3 748 277 (J.G.WAGNER) *Column 5, lines 43-75; column 6, lines 1-15,69-75; column 7, lines 18-23; column 12, lines 33-35; column 13, lines 4-15; column 15, lines 70-72*	1,2,3, 4,6,7	TECHNICAL FIELDS SEARCHED (Int. Cl. 7) B 01 J A 61 K
A	--- US-A-3 354 863 (J.B.REYNOLDS) *Column 6, lines 5-17*	1,2,3	
A	--- GB-A-1 371 840 (MERCK & CO.) *Page 2, lines 65-80; page 2, lines 43-94*	1,4,7	

The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 07-01-1983	Examiner KERRES P.M.G.
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	

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